CHAPTER 19

Urothelial and kidney cancers

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UROTHELIAL CANCER

In the year 2005, an estimated 63,210 new cases of bladder cancer will be diagnosed in the United States, and approximately 13,180 patients will die of this disease.

Urothelial cancers encompass carcinomas of the bladder, ureters, and renal pelvis; these cancers occur at a ratio of 50:3:1, respectively. Cancer of the urothelium is a multifocal process. Patients with cancer of the upper urinary tract have a 30%-50% chance of developing cancer of the bladder at some time in their lives. On the other hand, patients with bladder cancer have a 2%-3% chance of developing cancer of the upper urinary tract. The incidence of renal pelvis tumors is decreasing.

Epidemiology

Gender Urothelial cancers occur more commonly in men than in women (3:1) and have a peak incidence in the seventh decade of life.

Race Cancers of the urothelial tract are also more common in whites than in blacks (2:1).

Etiology and risk factors

Cigarette smoking The major cause of urothelial cancer is cigarette smoking. A strong correlation exists between the duration and amount of cigarette smoking and cancers at all levels of the urothelial tract. This association holds for both transitional cell and squamous cell carcinomas.

Analgesic abuse Abuse of compound analgesics, especially those containing phenacetin, has been associated with an increased risk of cancers of the urothelial tract. This risk appears to be greatest for the renal pelvis, and cancer at this site is usually preceded by renal papillary necrosis. The risk associated with analgesic abuse is seen after the consumption of excessive amounts (5 kg).

Chronic urinary tract inflammation also has been associated with urothelial cancers. Upper urinary tract stones are associated with renal pelvis cancers.

Chronic bladder infections can predispose patients to cancer of the bladder, usually squamous cell cancer.

Occupational exposures have been associated with an increased risk of urothelial cancers. Workers exposed to arylamines in the organic chemical, rubber, and paint and dye industries have an increased risk of urothelial cancer similar to that originally reported for aniline dye workers.

Balkan nephropathy An increased risk of cancer of the renal pelvis and ureters occurs in patients with Balkan nephropathy. This disorder is a familial nephropathy of unknown cause that results in progressive inflammation of the renal parenchyma, leading to renal failure and multifocal, superficial, low-grade cancers of the renal pelvis and ureters.

Genetic factors There are reports of families with a higher risk of transitional cell cancers of the urothelium, but the genetic basis for this familial clustering remains undefined.

Signs and symptoms

Hematuria is the most common symptom in patients presenting with urothelial tract cancer. It is most often painless, unless obstruction due to a clot or tumor and/or deeper levels of tumor invasion have already occurred.

Urinary voiding symptoms of urgency, frequency, and/or dysuria are also seen in patients with cancers of the bladder or ureters but are uncommon in patients with cancers of the renal pelvis.

Vesical irritation without hematuria can be seen, especially in patients with carcinoma in situ of the urinary bladder.

Symptoms of advanced disease Pain is usually a symptom of more advanced disease, as is edema of the lower extremities secondary to lymphatic obstruction.

Diagnosis

Initial work-up The initial evaluation of a patient suspected of having urothelial cancer consists of excretory urography, followed by cystoscopy. In patients with upper tract lesions, retrograde pyelography can better define the exact location of lesions. Definitive urethroscopic examination and biopsy can be accomplished utilizing rigid or flexible instrumentation.

At the time of cystoscopy, urine is obtained from both ureters for cytology, and brush biopsy is obtained from suspicious lesions of the ureter. Brush biopsies significantly increase the diagnostic yield over urine cytology alone. Also, at the time of cystoscopy, a bimanual examination is performed to determine whether a palpable mass is present and whether the bladder is mobile or fixed.

Evaluation of a primary bladder tumor In addition to biopsy of suspicious lesions, evaluation of a bladder primary tumor includes biopsy of selected mucosal sites to detect possible concomitant carcinoma in situ. Biopsies of the

primary lesion must include bladder wall muscle to determine whether there is invasion of muscle by the overlying carcinoma.

CT For urothelial cancers of the upper tract or muscle invasive bladder cancers, a CT scan of the abdomen/pelvis is performed to detect local extension of the cancer and involvement of the abdominal lymph nodes.

Bone scan For patients with bone pain or an elevated alkaline phosphatase level, a radioisotope bone scan is performed.

A chest x-ray completes the staging evaluation.

Pathology

Transitional cell carcinomas constitute 90%-95% of urothelial tract cancers.

Squamous cell cancers account for 3%-7% of urothelial carcinomas and are more common in the renal pelvis and ureters.

Adenocarcinomas account for a small percentage (< 3%) of bladder malignancies and are predominantly located in the trigone region. Adenocarcinomas of the bladder that arise from the dome are thought to be urachal in origin.

Carcinoma in situ In approximately 30% of newly diagnosed bladder cancers, there are multiple sites of bladder involvement, most commonly with carcinoma in situ. Although carcinoma in situ can occur without macroscopic cancer, it most commonly accompanies higher disease stages.

When carcinoma in situ is associated with superficial tumors, rates of recurrence and disease progression (development of muscle invasion) are higher (50%-80%) than when no such association is present (10%). Carcinoma in situ involving the bladder diffusely without an associated superficial tumor is also considered an aggressive disease. Most patients with this type of cancer will develop invasive cancers of the bladder.

Staging and prognosis

Staging system Urothelial tract cancers are staged according to the American Joint Committee on Cancer (AJCC) TNM classification system (Table 1). Superficial bladder cancer includes papillary tumors that involve only the mucosa (Ta) or submucosa (T1) and flat carcinoma in situ (Tis). The natural history of superficial bladder cancer is unpredictable, and recurrences are common. Most tumors recur within 6-12 months and are of the same stage and grade, but 10%-15% of patients with superficial cancer will develop invasive or metastatic disease.

Prognostic factors For carcinomas confined to the bladder, ureters, or renal pelvis, the most important prognostic factors are T stage and differentiation pattern. The impact of associated carcinoma in situ on Ta and T1 lesions is discussed above (see section on "Pathology"). Less-differentiated Ta-T1 lesions also are associated with higher recurrence and progression rates. Patients with well-differentiated Ta lesions without carcinoma in situ have a 95%

TABLE 1: TNM staging of urothelial tract cancers

Primary tumor (T)		
Tx		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Ta		Noninvasive papillary tumor
Tis		Carcinoma in situ: "flat tumor"
T1		Tumor invades subepithelial connective tissue
T2		Tumor invades muscle
	pT2a	Tumor invades superficial muscle (inner half)
	pT2b	Tumor invades deep muscle (outer half)
T3		Tumor invades perivesical tissue
	pT3a	Microscopically
	pT3b	Macroscopically (extravesical mass)
T4		Tumor invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall
	T4a	Tumor invades prostate, uterus, vagina
	T4b	Tumor invades pelvic wall, abdominal wall
Regional lymph nodes (N)		
Nx		Regional lymph nodes cannot be assessed
N0		No regional node involvement
N1		Metastasis in a single node, ≤ 2 cm in greatest dimension
N2		Metastasis in a single node, > 2 cm but ≤ 5 cm in greatest dimension; or multiple lymph nodes, none > 5 cm in greatest dimension
N3		Metastasis in a lymph node, > 5 cm in greatest dimension
Distant metastasis (M)		
Mx		Distant metastasis cannot be assessed
M0		No distant metastasis
M1		Distant metastasis

Stage grouping			
Stage 0a	Ta	N0	M0
Stage 0is	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2a	N0	M0
	T2b	N0	M0
Stage III	T3a	N0	M0
	T3b	N0	M0
	T4a	N0	M0
Stage IV	T4b	N0	M0
	Any T	N1-N3	M0
	Any T	Any N	M1

From Greene FL, Page DL, Fleming ID, et al (eds): AJCC Cancer Staging Manual, 6th ed. New York, Springer-Verlag, 2002.

survival rate, whereas those with high-grade T1 lesions have a 10-year survival rate of 50%.

Muscle invasive carcinoma carries a 5-year survival rate of 20%-50%. When regional lymph nodes are involved, the 5-year survival rate is 0%-20%.

Treatment

TREATMENT OF LOCALIZED DISEASE

Surgical approaches to superficial bladder cancer

Transurethral resection Most patients with superficial bladder cancer can be treated adequately with transurethral resection (TUR). Such procedures preserve bladder function, entail minimal morbidity, and can be performed repeatedly. Survival rates > 70% at 5 years are expected. Although TUR removes existing tumors, it does not prevent the development of new lesions. Patients should be followed closely.

Laser The neodymium:yttrium-aluminum-garnet (Nd:YAG) laser has achieved good local control when used in the treatment of superficial bladder tumors. However, it has not been adopted for general use because of its limitations in obtaining material for staging and grading of tumors.

Partial cystectomy is an infrequently utilized treatment option for patients whose tumors are not accessible or amenable to TUR.

Radical cystectomy is generally not used for the treatment of superficial bladder tumors. The indications for radical cystectomy include:

- Unusually large tumors that are not amenable to complete TUR, even on repeated occasions
- Some high-grade tumors
- Multiple tumors or frequent recurrences that make TUR impractical
- Symptomatic diffuse carcinoma in situ (Tis) that proves unresponsive to intravesical therapy
- Prostatic stromal involvement.

Intravesical therapy The indications for intravesical therapy include:

- Stage T1 tumors, especially if multiple
- Multifocal papillary Ta lesions, especially grade 2 or 3
- Diffuse carcinoma in situ (Tis)
- Rapidly recurring Ta, T1, or Tis disease.

In the United States, four intravesical agents are commonly used: thiotepa, an alkylating agent; bacillus Calmette-Guérin (BCG), an immune modulator/stimulator; and mitomycin (Mutamycin) and doxorubicin, both antibiotic chemotherapeutic agents. The dose of BCG varies with the strain (50 mg [Tice] or 60 mg [Connaught]). Mitomycin doses range from 20 to 40 mg.

Although all four agents reduce the tumor recurrence rate, BCG is the most effective. For the treatment of papillary Ta and T1 lesions, BCG and mitomycin have the greatest efficacy (complete response rate, approximately 50%). For the treatment of carcinoma in situ (Tis), BCG is extremely effective.

Surgical approaches to invasive bladder cancer

Radical cystectomy Invasive bladder cancer (stage II or higher) is best treated by radical cystectomy. Candidates for radical cystectomy include:

- Patients with muscle-invasive tumor (depth of invasion is not important, merely its presence), regardless of grade
- Patients with high-grade, invasive, lamina propria tumors with evidence of lymphovascular invasion, with or without carcinoma in situ (Tis)
- Patients with diffuse carcinoma in situ or recurrent superficial cancer who do not respond to intravesical therapy.

In men, radical cystectomy includes en bloc pelvic lymph node dissection and removal of the bladder, seminal vesicles, and prostate. In women, radical cystectomy entails en bloc pelvic lymph node dissection and anterior exenteration, including both ovaries, fallopian tubes, uterus, cervix, anterior vaginal wall, bladder, and urethra.

Partial cystectomy is an infrequently utilized treatment option and should only be considered when there is a solitary lesion in the dome of the bladder and when random biopsy results from remote areas of the bladder and prostatic urethra are negative.

Urethrectomy is routinely included in the anterior exenteration performed in female patients. Urethrectomy in male patients is performed if the tumor grossly involves the prostatic urethra or if prior TUR biopsy results of the prostatic stroma are positive. Delayed urethrectomy for positive urethral cytology or biopsy is required in about 10% of male patients.

Urinary reconstruction may involve any one of the following: intestinal conduits (eg, ileal, jejunal, or colonic), continent cutaneous diversion (eg, Indiana pouch, Kock pouch), or orthotopic reconstruction (in both male and female patients).

Surgical approaches to ureteral and renal pelvic tumors

Optimal surgical management of urothelial malignancies of the ureter and renal pelvis consists of nephroureterectomy with excision of a bladder cuff. Some tumors may respond well to local resection, and tumor specifics may allow for a more conservative intervention.

Upper ureteral and renal pelvic tumors (because of similar tumor behavior and anatomic aspects) may be considered as a group, whereas lower ureteral tumors may be considered as a separate group.

Upper ureteral and renal pelvic tumors are best treated with nephroureterectomy. Solitary, low-grade upper tract tumors may be considered for seg-

mental excision or ureteroscopic surgery if close surveillance is feasible. Care should be exercised, however, as multicentricity is more probable and the risk of recurrence is greater than for lower ureteral lesions.

Lower ureteral lesions may be managed by nephroureterectomy, segmental resection, and neovesical reimplantation or by endoscopic resection. A 15% recurrence rate is seen after segmental resection or endoscopic excision. Careful follow-up is mandatory. Disease progression, the development of a ureteral stricture precluding periodic surveillance, and poor patient compliance are indications to abandon conservative management and perform nephroureterectomy.

ROLE OF RADIATION THERAPY

Radiation therapy for bladder cancer

Primary radiation or chemoradiation therapy Radiation therapy, either alone or in conjunction with chemotherapy, is the modality of choice for patients whose clinical condition precludes surgery, either because of extensive disease or poor overall status. Trials have shown that patients treated with irradiation and cisplatin with or without fluorouracil (5-FU) have improved local control, as compared with patients treated with irradiation alone.

Other studies suggest that TUR followed by radiation therapy combined with cisplatin or 5-FU chemotherapy, with cystectomy reserved for salvage, provides a survival equivalent to that achieved with initial radical cystectomy while allowing for bladder preservation in many patients. The extent of TUR and the absence of hydronephrosis are important prognostic factors in studies of bladder-conserving treatment. Updates from institutions in Europe and the United States on over 600 patients with long-term follow-up support the durability of outcomes previously reported.

A randomized phase III study of bladder preservation with or without neoadjuvant chemotherapy following TUR, conducted by the Radiation Treatment Oncology Group (RTOG), revealed no advantage to the use of MCV (methotrexate, cisplatin, and vinblastine) before radiation therapy and concurrent cisplatin. The favorable outcome without neoadjuvant chemotherapy may make bladder preservation a more acceptable option for a wider range of patients.

Preoperative irradiation may improve survival in patients undergoing radical cystectomy. Its use is limited due to concern over complications occurring with the urinary diversions currently utilized.

Radiation dose and technique Initially, a pelvic field is treated to 4,500 cGy utilizing a four-field box technique, with 180 cGy delivered daily. The bladder tumor is then boosted to a total dose of 6,480 cGy utilizing multifield techniques, with 180 cGy delivered daily.

TABLE 2: Chemotherapy regimens for bladder carcinoma

Drug/combination	Dose and schedule
M-VAC	
Methotrexate	30 mg/m^2 IV on days 1, 15, and 22
Vinblastine	3 mg/m^2 IV on days 2, 15, and 22
Adriamycin (doxorubicin)	30 mg/m^2 IV on day 2
Cisplatin	70 mg/m^2 IV on day 2
NOTE: Reduce doxorubicin dose to 15 mg/m^2 in patients who have received prior pelvic irradiation. On days 15 and 22, methotrexate (30 mg/m^2) and vinblastine (3 mg/m^2) are given only if the WBC count is > 2,500 cells/mL and the platelet count is > 100,000 cells/mL.	
Repeat cycles every 28-32 days even if the interim dose is withheld due to myelosuppression or mucositis.	
Loehrer PJ Sr, Einhorn LH, Elson PJ, et al: J Clin Oncol 10:1066–1073, 1992.	
Paclitaxel/carboplatin	
Paclitaxel	200 mg/m^2 IV infused over 3 hours
Carboplatin	Dose calculated by the Calvert formula to an area under the curve (AUC) of 5 mg/mL/min IV infused over 15 minutes after paclitaxel
Repeat cycle every 21 days.	
PREMEDICATIONS: Dexamethasone, 20 mg PO, 12 and 6 hours prior to paclitaxel; as well as ranitidine, 50 mg IV, and diphenhydramine, 50 mg IV, both 30-60 minutes prior to paclitaxel.	
Redman B, Smith D, Flaherty L, et al: J Clin Oncol 16:1844–1848, 1998.	
Gemcitabine/cisplatin	
Gemcitabine	1 g/m^2 IV on days 1, 8, and 15
Cisplatin	75 mg/m^2 IV on day 1
Repeat cycle every 28 days.	
Kaufman D, Stadler W, Carducci M, et al: Proc Am Soc Clin Oncol 17:320a, 1998.	

Radiation therapy for renal pelvic and ureteral cancers

In patients with renal pelvic and ureteral lesions who have undergone nephroureterectomy, postoperative local-field irradiation is offered if there is periureteral, perirenal, or peripelvic extension or lymph node involvement. A dose of approximately 4,500-5,040 cGy is delivered utilizing multifield techniques.

Palliative irradiation

Palliative radiation therapy is effective in controlling pain from local and metastatic disease and in providing hemostatic control. A randomized study comparing 3,500 cGy in 10 fractions vs 2,100 cGy in 3 hypofractionated treatments revealed high rates of relief of hematuria, frequency, dysuria, and nocturia with either regimen. In selected cases of bladder cancer, aggressive palliation to approximately 6,000 cGy may be warranted to provide long-term local control. Concurrent chemotherapy, such as cisplatin, should be considered.

Drug/combination	Dose and schedule
PCG	
Paclitaxel	200 mg/m^2 IV infused over 3 hours on day 1
Carboplatin	Dose calculated on AUC of 5, 15-minute IV infusion on day 1
Gemcitabine	800 mg/m^2 30-minute IV on days 1 and 8
Repeat cycle every 21 days.	
PREMEDICATIONS: Dexamethasone, 20 mg PO, 12 and 6 hours prior to paclitaxel; diphenhydramine, 50 mg IV, 30 minutes prior to paclitaxel; and either cimetidine, 300 mg IV, or ranitidine, 50 mg IV, 30 minutes prior to paclitaxel.	
Hussain M, Vaishampayan U, Du W, et al: J Clin Oncol 19:2527–2533, 2001.	
Paclitaxel/cisplatin	
Paclitaxel	135 mg/m^2 IV infused over 3 hours
Cisplatin	70 mg/m^2 IV infused over 2 hours
Repeat cycle every 3 weeks until disease progression or for a maximum of 6 cycles.	
PREMEDICATIONS: Dexamethasone, 20 mg PO, 12 and 6 hours prior to paclitaxel; as well as ranitidine, 50 mg IV, or cimetidine, 300 mg IV, prior to paclitaxel, and diphenhydramine, 50 mg IV, 30 minutes prior to paclitaxel.	
Burch PA, Richardson RI, Cha SS, et al: Proc Am Soc Clin Oncol 18:1266a, 1999.	
TCG	
Taxol (paclitaxel)	80 mg/m^2 IV infused over 1 hour on days 1 and 8
Cisplatin	70 mg/m^2 on day 1
Gemcitabine	1 g/m^2 IV on days 1 and 8
Repeat cycle every 21 days.	
PREMEDICATIONS: Dexamethasone, 20 mg PO, 12 and 6 hours prior to paclitaxel; as well as diphenhydramine, 50 mg IV, 30 minutes prior to paclitaxel, and either cimetidine, 300 mg IV, or ranitidine, 50 mg IV, 30 minutes prior to paclitaxel.	
Vaishampayan U, Smith D, Redman B, et al: Proc Am Soc Clin Oncol 18:333a (abstract 1282), 1999.	
Table prepared by Ishmael Jaiyesimi, DO	

CHEMOTHERAPY FOR ADVANCED DISEASE

Treatment of advanced metastatic urothelial cancer is palliative. Cisplatin, paclitaxel, and gemcitabine (Gemzar) have all demonstrated single-agent activity for the systemic treatment of this disease. A randomized trial showed an advantage for a regimen of M-VAC (methotrexate, vinblastine, Adriamycin [doxorubicin], and cisplatin) over cisplatin alone with regard to disease progression-free and overall survival. Combination regimens with cisplatin or carboplatin (Paraplatin), usually with paclitaxel or gemcitabine or in combination with methotrexate and vinblastine with or without doxorubicin, produce

response rates of 40%-60% in patients with advanced disease, with a median survival of 12-14 months (Table 2). In another randomized trial, the combination of gemcitabine and cisplatin exhibited equivalent survival to M-VAC in metastatic bladder cancer but was clinically better tolerated. The role of combination chemotherapy in the adjuvant treatment of resected urothelial cancer remains undetermined and an area of clinical research. A randomized trial of neoadjuvant M-VAC in locally advanced resectable bladder cancer showed a trend in survival favoring M-VAC over surgery alone, but it was not statistically significant.

KIDNEY CANCER

Approximately 36,160 new cases of renal cell carcinoma will be diagnosed in the year 2005 in the United States, with an associated 12,660 deaths. There has been a steady increase in the incidence of renal cell carcinoma that is not explained by the increased use of diagnostic imaging procedures. Mortality rates have also shown a steady increase over the past 2 decades.

Epidemiology

Gender and age This malignancy is twice as common in men as in women. Most cases of renal cell carcinoma are diagnosed in the fourth to sixth decades of life, but the disease has been reported in all age groups.

Ethnicity Renal cell carcinoma is more common in persons of northern European ancestry than in those of African or Asian descent.

Etiology and risk factors

Renal cell carcinoma occurs most commonly as a sporadic form and rarely as a familial form. The exact etiology of sporadic renal cell carcinoma has not been determined. However, smoking, obesity, and renal dialysis have been associated with an increased incidence of the disease.

Genetic factors More recently, a genetic basis has been sought for this disease.

von Hippel-Lindau disease, an autosomal-dominant disease, is associated with retinal angiomas, CNS hemangioblastomas, and renal cell carcinoma.

Chromosomal abnormalities Deletions of the short arm of chromosome 3 (3p) occur commonly in renal cell carcinoma associated with von Hippel-Lindau disease. In the rare familial forms of renal cell carcinoma, translocations affecting chromosome 3p are uniformly present. Sporadic renal cell carcinoma of the nonpapillary type is also associated with 3p deletions.

Associated malignancy Two studies from large patient databases have reported a higher-than-expected incidence of both renal cell cancer and lymphoma. No explanation for this association has been found.

Signs and symptoms

Renal cell carcinoma has been associated with a wide array of signs and symptoms. The classic triad of hematuria, flank mass, and flank pain occurs in only 10% of patients and is usually associated with a poor prognosis. With the routine use of CT scanning for various diagnostic reasons, renal cell carcinoma is being diagnosed more frequently as an incidental finding.

Hematuria More than half of patients with renal cell carcinoma present with hematuria.

Other common signs/symptoms Other commonly associated signs and symptoms of renal cell carcinoma include normocytic/normochromic anemia, fever, and weight loss.

Less common signs/symptoms Less frequently occurring, but often described, signs and symptoms include polycythemia, hepatic dysfunction not associated with hepatic metastasis, and hypercalcemia. Although not a common finding at the time of diagnosis of renal cell carcinoma, hypercalcemia ultimately occurs in up to 25% of patients with metastatic disease.

Diagnosis

Contrast-enhanced CT scanning has virtually replaced excretory urography and renal ultrasonography in the evaluation of suspected renal cell carcinoma. In most cases, CT imaging can differentiate cystic from solid masses and also supplies information about lymph nodes and renal vein/inferior vena cava (IVC) involvement.

Ultrasonography is useful in evaluating questionable cystic renal lesions if CT imaging is inconclusive.

Venography and MRI When IVC involvement by tumor is suspected, either IVC venography or MRI is needed to evaluate its extent. MRI is currently the preferred imaging technique for assessing IVC involvement at most centers.

Renal arteriography is not used as frequently now as it was in the past in the evaluation of suspected renal cell carcinoma. In patients with small, indeterminate lesions, arteriography may be helpful. It is also used by the surgeon as part of the preoperative evaluation of a large renal neoplasm.

Percutaneous cyst puncture is used in the evaluation of cystic renal lesions that are thought to be potentially malignant on the basis of ultrasonography or CT imaging. Percutaneous cyst puncture permits the collection of cyst fluid for analysis, as well as the evaluation of cyst structure via instillation of contrast medium after fluid removal. Benign cyst fluid is usually clear to straw-colored and low in protein, fat, and lactic dehydrogenase (LDH) content, whereas malignant fluid is usually bloody with high protein, fat, and LDH content.

Evaluation of extra-abdominal disease sites includes a chest x-ray. In the face of a normal chest x-ray, CT imaging of the chest adds no further helpful

information. A bone scan is required if a patient has symptoms suggestive of bone metastasis and/or an elevated alkaline phosphatase level.

Pathology

Renal cell carcinoma arises from the proximal renal tubular epithelium. Histologically, renal cell carcinoma can be of various cellular types: clear cell, granular cell, and sarcomatoid (spindle) variant. The majority of these tumors are mixtures of clear and granular cell types. Approximately 1%-6% of renal cell carcinomas are of the sarcomatoid variant, which is a more aggressive malignancy with a worse prognosis.

Staging and prognosis

Staging system The preferred staging system for renal cell carcinoma is the TNM classification (Table 3).

Prognostic factors The natural history of renal cell carcinoma is highly variable. However, approximately 30% of patients present with metastatic disease at diagnosis, and one-third of the remainder will develop metastasis during follow-up.

Five-year survival rates after nephrectomy for tumors confined to the renal parenchyma (T1/2) are > 80%. Renal vein involvement without nodal involvement does not affect survival. Lymph node involvement and/or extracapsular spread is associated with a 5-year survival of 10%-25%. Patients with metastatic disease have a median survival of 1 year and a 5-year survival of 0%-20%.

Treatment

Surgery

Radical nephrectomy is the established therapy for localized renal cell carcinoma. At surgery, the kidneys, adrenal gland, and perirenal fat (structures bound by Gerota's fascia) are removed. Also, limited regional lymph node dissection is often performed for staging purposes. Partial nephrectomy is considered in patients for whom a radical nephrectomy would result in permanent dialysis.

Since complete resection is the only known cure for renal cell carcinoma, even in locally advanced disease, surgery is considered if the involved structures can be safely removed. In the presence of metastatic disease, surgery is generally considered for palliation only. However, in patients with metastatic disease who are candidates for cytokine therapy and have a good performance status, a debulking nephrectomy may benefit survival by several months.

Radiation therapy for renal cell carcinoma

Primary radiation therapy Radiation therapy may be considered for palliation as the primary therapy for renal cell carcinoma in patients whose clinical

TABLE 3: TNM staging of renal cell carcinoma

Primary tumor (T)		
Tx		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1		Tumor ≤ 7 cm in greatest dimension, limited to the kidneys
	T1a	Tumor ≤ 4 cm in greatest dimension, limited to the kidneys
	T1b	Tumor > 4 cm but not > 7 cm in greatest dimension, limited to the kidneys
T2		Tumor > 7 cm in greatest dimension, limited to the kidneys
T3		Tumor extends into major veins or invades adrenal gland or perinephric tissues but not beyond Gerota's fascia
	T3a	Tumor directly invades adrenal gland or perirenal and/or renal sinus fat but not beyond Gerota's fascia
	T3b	Tumor grossly extends into renal vein or its segmental (muscle-containing) branches or vena cava below the diaphragm
	T3c	Tumor grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava
T4		Tumor invades beyond Gerota's fascia
Regional lymph nodes (N)		
Nx		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Metastasis in a single regional lymph node
N2		Metastasis in more than one regional lymph node
Distant metastasis (M)		
Mx		Distant metastasis cannot be assessed
M0		No distant metastasis
M1		Distant metastasis

Stage grouping			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1	N1	M0
	T2	N1	M0
	T3a	N0-N1	M0
	T3b	N0-N1	M0
	T3c	N0-N1	M0
Stage IV	T4	N0-N1	M0
	Any T	N2	M0
	Any T	Any N	M1

From Greene FL, Page DL, Fleming ID, et al (eds): AJCC Cancer Staging Manual, 6th ed. New York, Springer-Verlag, 2002.

TABLE 4: Biologic therapy regimens for renal cell carcinoma

Dose and schedule
High-dose IL-2
IL-2: 600,000 or 720,000 IU/kg IV infused over 15 minutes every 8 hours until toxicity develops; or 14 consecutive doses for 5 days
After a 5- to 9-day rest period, an additional 14 doses of IL-2 are administered over a 5-day period. If patients show evidence of tumor regression or stable disease, 1-2 more courses of treatment may be given.
Fyfe G, Fisher RI, Rosenberg SA, et al: J Clin Oncol 13:688–696, 1995.
Low-dose IL-2
IL-2: 72,000 IU/kg by IV bolus every 8 hours to a maximum of 15 doses every 7-10 days for 2 cycles
NOTE: The cycles represent one course of therapy. Patients who are stable or responding after one course of therapy receive a second course. Third and fourth courses are given only if patients demonstrate further tumor regression.
Yang JC, Topalian SL, Parkinson D, et al: J Clin Oncol 12:1572–1576, 1998.

Table prepared by Ishmael Jaiyesimi, DO

condition precludes surgery, either because of extensive disease or poor overall condition. A dose of 4,500 cGy is delivered, with consideration of a boost up to 5,500 cGy.

Postoperative radiation therapy is controversial. However, it may be considered in patients with perinephric fat extension, adrenal invasion, or involved margins. A dose of 4,500 cGy is delivered, with consideration of a boost.

Palliation Radiation therapy is commonly used for palliation for metastatic and local disease.

Systemic therapy for advanced disease

Metastatic renal cell carcinoma is resistant to chemotherapeutic agents. An extensive review of currently available agents concluded that the overall response rate to chemotherapy is 6%.

Interleukin-2 The only FDA-approved treatment for metastatic renal cell carcinoma is high-dose interleukin-2 (IL-2, aldesleukin [Proleukin]; Table 4).

High-dose regimen High-dose IL-2 (720,000 IU/kg IV piggyback every 8 hours for 14 doses, repeated once after a 9-day rest) results in a 15% remission rate (7% complete responses, 8% partial responses). The majority of responses to IL-2 are durable, with a median response duration of 54 months.

The major toxicity of high-dose IL-2 is a sepsis-like syndrome, which includes a progressive decrease in systemic vascular resistance and an associated decrease in intravascular volume due to a "capillary leak." Management includes judicious use of fluids and vasopressor support to maintain blood pressure and intravascular volume and at the same time to avoid pulmonary toxicity due to noncardiogenic

pulmonary edema from the capillary leak. This syndrome is totally reversible.

Other doses and schedules Because of the toxicity of high-dose IL-2, other doses and schedules have been and are being evaluated. Several trials of low-dose IL-2 (3-18 $\times$ 10^6 IU/d), either alone or combined with interferon alfa (Intron A, Roferon-A), have reported response rates similar to those achieved with high-dose IL-2. Patients should be encouraged to participate in ongoing clinical trials of metastatic renal cell carcinoma.

SU011248 and BAY 43-9006 are novel agents under development, with early reports showing activity in advanced kidney cancer. These agents block angiogenic pathways as well as pathways important in cell proliferation. Initial reports have shown partial response and prolonged disease stabilization (*Motzer RJ, Rini BI, Michaelson MD, et al: Proc Am Soc Clin Oncol [abstract] 23:381, 2004; Ratain MJ, Flaherty KT, Stadler WM, et al: Proc Am Soc Clin Oncol [abstract] 23:381, 2004*).

Immunotherapy New immunotherapeutic approaches under investigation for the treatment of advanced renal cell cancer include the use of peripheral blood stem cell transplantations, dendritic cell-based vaccines, and monoclonal antibodies. Early reports on the use of allogeneic stem cell transplantation from HLA-matched donors to invoke a graft-vs-tumor reaction have shown encouraging preliminary results that warrant further investigation. A humanized monoclonal antibody against the G250 antigen found on all clear cell, and the majority of nonclear cell, renal carcinomas is also in clinical trials.

Another area of promising therapeutic clinical research in advanced renal cell cancer is the evaluation of antiangiogenic factors. Most renal cell carcinomas are highly vascular tumors, and inhibition of tumor neovascularity holds new promise for better treatments.

SUGGESTED READING

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